

CHRONIC TOXICITY SUMMARY

# HYDRAZINE

(diamine; diamide; nitrogen hydride; levoxine)

CAS Registry Number: 302-01-2

## I. Chronic Toxicity Summary

<i>Inhalation reference exposure level</i>	<b>0.2 <math>\mu\text{g}/\text{m}^3</math></b> (0.1 ppb)
<i>Critical effect(s)</i>	Amyloidosis of the liver and thyroid in hamsters
<i>Hazard index target(s)</i>	Alimentary system; endocrine system

## II. Chemical Property Summary (HSDB, 1995; CRC, 1994)

<i>Description</i>	Colorless, oily liquid or white crystals
<i>Molecular formula</i>	$\text{N}_2\text{H}_4$
<i>Molecular weight</i>	32.05 g/mol
<i>Boiling point</i>	113.5°C (Merck, 1983; CRC, 1994)
<i>Melting point</i>	2.0°C
<i>Vapor pressure</i>	14.4 torr @ 25°C
<i>Solubility</i>	Miscible with water, methyl-, ethyl-, isobutyl alcohols; slightly miscible with hydrocarbons; insoluble in chloroform, ether
<i>Conversion factor</i>	1.31 $\mu\text{g}/\text{m}^3$ per ppb at 25°C

## III. Major Uses and Sources

Hydrazine is a highly reactive base and reducing agent. Its primary uses are as a high-energy rocket propellant, as a reactant in military fuel cells, in nickel plating, in the polymerization of urethane, for removal of halogens from wastewater, as an oxygen scavenger in boiler feedwater to inhibit corrosion, and in photographic development (Von Burg and Stout, 1991). Hydrazine was historically used experimentally as a therapeutic agent in the treatment of tuberculosis, sickle cell anemia, and non-specific chronic illnesses (Von Burg and Stout, 1991; Gold, 1987). The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 1664 pounds of hydrazine (CARB, 2000).

#### **IV. Effects of Human Exposure**

One person was occupationally exposed to hydrazine at unknown levels once per week for a period of 6 months (Sotaniemi *et al.*, 1971). The worker showed symptoms of conjunctivitis, tremors, and lethargy for 1-2 days following each exposure. Vomiting, fever, and diarrhea developed on the last day of exposure and progressed to abdominal pain and incoherence. The previously healthy 59-year old individual died three weeks after the last exposure. Evidence of tracheitis, bronchitis, heart muscle degeneration, and liver and kidney damage was found at autopsy. A single case report can not prove a cause and effect relationship between hydrazine exposures and the noted symptoms and death, but the repeated association between exposures and symptoms is highly suspicious. Liver toxicity is also associated with acute exposure to hydrazine.

The only epidemiological studies of human hydrazine exposures found involve workers in a hydrazine manufacturing plant (Wald *et al.*, 1984; Wald, 1985; Morris *et al.*, 1995). Workers were exposed to various durations of at least 6 months between 1945 and 1972 and have been followed through 1992. The studies are based on a review of medical records. Only 78 of 427 workers were believed to have had more than incidental exposure to hydrazine. Only cumulative mortality was reviewed. Health effects reported during or after hydrazine exposure were not examined. No increase in mortality was noted for lung cancer, other cancers, or causes other than cancer. However, these small studies have little power to detect increased mortality, and age of death was not examined. The authors reported that relative risks up to 3.5 could have gone undetected.

Dermal sensitization has also been reported from repeated contact with hydrazine (Van Ketal, 1964; Von Keilig and Speer, 1983; Wrangsjö and Martensson, 1986).

#### **V. Effects of Animal Exposure**

An inhalation study of the toxicity and carcinogenicity of hydrazine was conducted in cats, mice, hamsters, and dogs (Vernot *et al.*, 1985). Various animal groups were exposed 6 hours/day, 5 days/weeks for one year to concentrations of 0.05, 0.25, 1.0, and 5.0 ppm anhydrous hydrazine base. Exposed and controls groups were made up of the following animals: 100 Fischer 344 rats/sex at 0.05, 0.25, 1.0, and 5.0 ppm hydrazine plus 150 rats/sex as controls; 400 female C57BL/6 mice at 0.05, 0.25, and 1.0 ppm hydrazine plus 800 female mice as controls; 200 male Golden Syrian hamsters at 0.25, 1.0, and 5.0 ppm hydrazine plus 200 male hamsters as controls; 4 beagle dogs/sex at 0.25 and 1.0 ppm hydrazine plus 4 dogs/sex as controls. Animals were observed post-exposure for the following periods: 18 months for rats, 15 months for mice, 12 months for hamsters, and 38 months for dogs. Animals were observed hourly during the exposure period and daily in the post-exposure period.

No non-cancer toxic effects were observed in mice or dogs, with the exception of a single dog, exposed to 1.0 ppm hydrazine, which showed cyclic elevations in serum glutamic-pyruvic transaminase levels and, upon necropsy at 36 months post-exposure, showed liver

effects described as “clusters of swollen hepatocytes that had highly vacuolated cytoplasm.” Of the other species examined, hamsters showed toxicity at the lowest dose levels, particularly amyloidosis in various organs including liver, spleen, kidney, thyroid, and adrenal glands. An increased incidence of amyloidosis was seen at the lowest exposure level (0.25 ppm hydrazine) in the liver and thyroid (67/160 exposed vs. 42/180 control for the liver and 20/117 exposed vs. 9/155 control in the thyroid;  $p \leq 0.01$  by Fisher’s exact test). This effect was found to be dose related. The incidence of hemosiderosis of the liver was also significantly increased in all exposed groups. Significantly increased incidences of toxic effects observed in the 1.0 and 5.0 ppm hydrazine groups include amyloidosis of the spleen, kidney glomerulus, and adrenals glands, and lymphadenitis of the lymph nodes. Significantly increased toxic effects observed only in the highest dose group include amyloidosis of the kidney interstitium and thyroid, and senile atrophy of the testis. The authors note these effects appear to reflect accelerated changes commonly associated with aging in hamsters.

Incidence of Nonneoplastic Lesions in Male Hamsters (from Table 3 of Vernot *et al.*)

<i>Lesion</i>	<i>Control</i>	<i>0.25 ppm</i>	<i>1.0 ppm</i>	<i>5.0 ppm</i>
Liver				
Amyloidosis	42/180 (23)*	67/160 (42) <sup>a</sup>	68/148 (46) <sup>a</sup>	79/159 (50) <sup>a</sup>
Hemosiderosis	42/180 (23)	63/160 (39) <sup>a</sup>	77/148 (52) <sup>a</sup>	94/159 (59) <sup>a</sup>
Bile duct hyperplasia	14/180 (8)	31/160 (19) <sup>a</sup>	28/148 (19) <sup>a</sup>	44/159 (28) <sup>a</sup>
Biliary cyst	45/180 (25)	45/160 (28)	42/148 (28)	55/159 (35) <sup>b</sup>
Thyroid				
Amyloidosis	9/155 (6)	20/117 (17) <sup>a</sup>	11/127 (9)	22/137 (16) <sup>a</sup>
Adrenal				
Amyloidosis	38/177 (22)	49/199 (32) <sup>b</sup>	52/141 (37) <sup>a</sup>	76/153 (50) <sup>a</sup>

\* Incidence of lesion (% of animals with lesion)

<sup>a</sup> Incidence significantly greater than control,  $p \leq 0.01$

<sup>b</sup> Incidence significantly greater than control,  $0.01 < p \leq 0.05$

In the hydrazine exposed rats, effects were observed in the respiratory tract of exposed animals. Specifically, squamous metaplasia of the larynx, trachea, and nasal epithelium (males only) was observed in the highest dose group (5.0 ppm hydrazine). Inflammation was also observed in the larynx and trachea of rats exposed to 5.0 ppm hydrazine. Increased incidence of focal cellular change of the liver was observed in female mice at 1.0 and 5.0 ppm hydrazine. Other effects with increased incidence only in the high dose group include hyperplastic lymph nodes in females, endometriosis, and inflammation of the uterine tube.

The toxic effects from inhalation of hydrazine over a six month period from both intermittent and continuous exposure scenarios were examined (Haun and Kinkead, 1973). Groups of 8 male beagle dogs, 4 female rhesus monkeys, 50 male Sprague-Dawley rats, and 40 female ICR rats per dose group were continuously exposed to 0.2 or 1.0 ppm hydrazine or intermittently (6 hours/day, 5 days/week) to 1.0 or 5.0 ppm hydrazine. A control group consisted of equal numbers of animals. The experimental design was such that each intermittent exposure group had a time-weighted-average matching continuous exposure group. Dose-related body weight reductions were observed in all treated groups as well as

evidence of hepatic degeneration, fatty deposition in the liver, central nervous system depression and lethargy, eye irritation, and anemia.

Toxic effects from the exposure of rats, mice, and dogs to airborne hydrazine at levels of 0, 4.6, or 14 ppm intermittently for 6 months were reported (Comstock *et al.*, 1954). Observed adverse effects included anorexia, irregular breathing, vomiting, fatigue, and emphysema in dogs; pulmonary congestion and emphysema in rats and mice; and lung and liver damage in rats.

Lymphoid bronchial hyperplasia was observed in guinea pigs exposed to 2-6 ppm hydrazine for 5 days/week for 19-47 days (Weatherby and Yard, 1955).

## VI. Derivation of Chronic Reference Exposure Level (REL)

<i>Study</i>	Vernot <i>et al.</i> , 1985
<i>Study population</i>	Hamster
<i>Exposure method</i>	Inhalation of 0, 0.25, 1, and 5 ppm
<i>Critical effects</i>	Amyloidosis and hemosiderosis of the liver; thyroid amyloidosis
<i>LOAEL</i>	0.25 ppm
<i>NOAEL</i>	Not observed
<i>Exposure continuity</i>	6 hour/day, 5 days/week
<i>Exposure duration</i>	1 year
<i>Average experimental exposure</i>	0.045 ppm for LOAEL group (0.25 x 6/24 x 5/7)
<i>Human equivalent concentration</i>	0.045 ppm for LOAEL group (gas with systemic effects, based on RGDR = 1.0 using default assumption that $\lambda(a) = \lambda(h)$ )
<i>LOAEL uncertainty factor</i>	10 (low incidence above controls but serious adverse effects)
<i>Subchronic uncertainty factor</i>	1
<i>Interspecies uncertainty factor</i>	3
<i>Intraspecies uncertainty factor</i>	10
<i>Cumulative uncertainty factor</i>	300
<i>Inhalation reference exposure level</i>	0.0001 ppm (0.1 ppb, 0.0002 mg/m <sup>3</sup> , 0.2 µg/m <sup>3</sup> )

Vernot *et al.* (1985) present a thorough examination of chronic health effects from inhalation exposure to hydrazine. This study was chosen for the development of the chronic reference exposure level because (1) it was conducted with an adequate number of animals, (2) the critical/sensitive adverse effect (degenerative change in the liver in hamsters) showed a dose-response relationship, and (3) the findings of this study support data found in studies by other groups.

This study shows a dose-related increase in the incidence of amyloidosis and hemosiderosis in hamsters intermittently exposed by inhalation to levels of hydrazine greater than 0.25 ppm. Other effects noted at 0.25 ppm included weight depression during exposure, mineralization

of the kidney, and amyloidosis of the thyroid. Haun and Kinkead (1973) have also noted lesions of the liver in dogs, monkeys, and mice exposed continuously to 0.2 ppm hydrazine for 6 months by inhalation. Comstock *et al.* (1954) observed liver damage in groups of rats exposed to hydrazine vapors. The single case report of hydrazine inhalation toxicity in humans showed necrosis and degeneration of the liver (Sotaniemi *et al.*, 1971).

## VII. Data Strengths and Limitations for Development of the REL

The strengths of the inhalation REL for hydrazine include the availability of chronic inhalation exposure data from a well-conducted study with histopathological analysis. Major areas of uncertainty are the lack of adequate human exposure data, the lack of reproductive and developmental toxicity studies, and the lack of observation of a NOAEL in the key study.

## VIII. References

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